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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/615,276	DIMATTEO ET AL.	
	Examiner	Art Unit	
	NABILA G. EBRAHIM	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15,17-27,29-33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15,17-27,29-33 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Applicant's amendments and arguments dated 4/15/2008is acknowledged.

Status of Claims:

Claims 1, 3-15, 17-27, 29-33, and 35-37 are pending in the application.

Status of Office Action: Final.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-10, 15, 17-27, 29-31 and 35-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. US 5888930 (Smith) in view of Gray PCT/AU2001/001370 (Gray), in view of Kaminski et al US 6015542 (hereinafter Kaminski).

Smith teaches controlled release beads of active ingredient in the pores of a polymeric micro-porous bead having an anisotropic pore structure of large pores in the interior and small pores at the surface, the gradation of pore sizes between the interior and the surface being continuous (abstract). The bead size is from 5 microns to 2 mm in diameter (col. 5, lines 3+). The micro porous beads are generally spherical in shape and have an anisotropic pore structure of large pores in the interior and small pores at the surface, the gradation of pore sizes between the interior and the surface being continuous (see abstract). Beads are typically loaded with active

ingredients, and the active ingredient is released at a slow and substantially constant rate over an extended period of time. the polymeric micro porous beads is made from a polymer selected from polycarbonates, polyamides, polyurethanes acrylic resins, polystyrene, polyolefin's, cellulose acetate and other cellulosic esters, ethylenevinyl alcohols (note that ethyleneviny alcohol particles are used as equivalents to polyvinyl alcohol particles. As evidenced by Y. Peirre Gobin et al., Head and Neck Hypervascular Lesions: Embolization with Ethylene Vinyl Alcohol Copolymer Laboratory Evaluation in Swine and Clinical Evaluation in Humans, 2001), and derivatives and copolymers of the above (see col. 2. lines 46- 65). And also, metals or other high- density particles such as inorganic solids can be loaded into the beads to increase the density (see col. 7, lines 36-39). And further, the beads after loading with active ingredient, they are coated with a separate nonporous polymeric coating to further retard release of active ingredient (see col. 7, lines 39-42). Smith meets the claim limitations as described above but fails to include the polymeric matrix comprises a cross-linked polymer.

Smith disclosed that a metal can be comprised in the pores of the disclosed beads, however, the reference is silent towards the use of radioisotopes.

Gray discloses a particulate material having a diameter in the range of from 5 to 200 microns (page 6) comprising a polymeric matrix and stably incorporated radionuclide, such as radioactive yttrium (page 1), processes for its production and a method of radiation therapy utilizing the particulate material (abstract). Gray used the compound for treating cancer; the therapeutic agent of instant claim 3 is interpreted as any compound that is used in the treatment of an ailment or a disease. Accordingly, Gray's compounds read also on claim 3. In addition, Gray disclosed that the radioisotope molecule is enclosed into the polymer bead (example 1). However, the method of preparation in example 1 does not exclude the possibility of having the drug on top of the polymer microspheres. The way of administration is by catheterization into

the hepatic artery via the femoral, or brachial artery (page 8, lines 10+). One of the objectives of the invention is to decrease leaching of radionuclides from the polymeric matrix, which can cause non-specific radiation of the patient and damage surrounding tissue. The goal amount of leaching reaches less than 0.4% (page 5, lines 11+). Gray teaches a method of preparation, which comprises the step of adding colorless solution of yttrium (90Y) sulfate to symmetrical microspheres of ion exchange resin (example 1.) The recitation of the polymer used in the particles is cross-linked, it is noted that Gray teaches that it is preferred that the polymeric matrix is partially cross linked (page 6, lines 8+).

It would have been obvious to one of ordinary skill in the art to comprise a radionuclide such as yttrium to the anisotropic structure of Smith because Smith teaches that asymmetric microporous beads are provided that can be prepared prior to loading them with active ingredient, that can contain up to 90% active ingredient, that are exceptionally durable and sprayable, and that can release essentially all of the active ingredient at a constant rate over long periods of time (col. 2, lines 18+).

Smith and Gray are deficient in disclosing an antibody bound to the isotope.

Kaminski et al. teaches a radioactively labeled monoclonal antibody or radioactively labeled monoclonal antibody fragment wherein said antibody or said antibody fragment binds to CD20 antigen present on the surface of cells (claim 1), which can be labeled with a radioisotope (example III) is used to treat cancers (col. 9, lines 7+).

A skilled man in the art would have been motivated at the time the invention was made to label a monoclonal antibody with a radioisotope to advance the treatment of cancers.
Claims 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. US 5888930 (Smith) in view of Gray in view of (Ajay, K. et al. 1993, *Extended preoperative polyvinyl*

alcohol microembolization of intracranial meningiomas: assessment of two embolization techniques, AJNR 14:571-582, May/Jun 1993) hereinafter “Ajay”.

Smith and Gray have been discussed above.

Both references did not disclose polyvinyl alcohol as the particle polymer.

Ajay evaluates the efficacy of preoperative meningioma devascularization with small polyvinyl alcohol (PVA) particles. The PVA particles are 150- 300 microns.

It would have been obvious to one of ordinary skill in the art to use Polyvinyl particles as a carrier for a radioisotope which may be attached to an antibody and use it for other types of cancers like gastrointestinal, lung, thyroid, or breast cancers and apply it to the anisotropic pore structure of Smith. The motivation would be the disclosed results of Ajay, which demonstrates that, the angiography after embolization using polyvinyl alcohol demonstrated the total elimination of tumor blush in all patients.

Claims 13-14 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. US 5888930 (Smith) in view of Gray and further in view of Atcher et al. US 4970062 hereinafter “Atcher”.

Smith and Gray have been discussed above.

Both references are deficient in disclosing the particles wherein the agent is attached to the surface of the particle.

Atcher teaches ferric hydroxide colloid having an alpha-emitting radionuclide essentially on the outer surfaces and a method of forming same. The method includes oxidizing a ferrous hydroxide to ferric hydroxide in the presence of a preselected radionuclide to form a colloid having the radionuclide on the outer surface thereof, and thereafter washing the colloid, and suspending the washed colloid in a suitable solution. The labeled colloid is useful in cancer therapy and for the treatment of inflamed joints. A colloid is defined as a system in which finely

divided particles, which are approximately 10 to 10,000 angstroms in size, are dispersed within a continuous medium in a manner that prevents them from being filtered easily or settled rapidly. Since Atcher describes a colloid, which is according to, the definition made of particles. It is understood that the radioisotope is attached to the outer surface of the particles (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to develop a particle made of a polymer in an anisotropic pore structure like Smith's and attach the radionuclide because Atcher discloses that the surface attached radionuclides can be used in cancer therapy. The artisan would have a good expectation of success of preparing a particle wherein a radionuclide is laid on the surface of the particle.

Finally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to advance the compositions and the methods disclosed by both Smith and Gray by using polyvinyl alcohol particles, an antibody specific for the type of cancer being treated, and the radionuclide as attached to the surface of the particle as disclosed by Atcher. It would have been further obvious to the skilled artisan to modify the methods and attach the radionuclide to the surface of the particle as disclosed by Atcher for the reasons and motivations set forth above. The expected results would be a composition used for gastrointestinal, and/or breast cancer therapy that comprise a polyvinyl polymer particle bound to a radionuclide, and an antibody. The radionuclide can be attached to the surface or encapsulated inside the polymer and the methods of production and use of the composition.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-15, 17-27, 29-33, and 35-37 areprovisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim3-5, 7-18, 21, 22, 24-34 and 39-41 of copending Application No. **10/232,265.** Although the conflicting claims are not identical, they are not patentably distinct from each other because US'276 claims a particle with a diameter of 1200 um or less which delivers a bioactive (see claim 1 and 3). The particles have pores, and comprise polyvinyl alcohol (see claims 11, 12, and 16). The pores have size greater size in the interior of the particle than on the outer portion of the particle (two regions). The particles may be used for treatment of various cancers (see claims 20 and 21). Administration may be by percutaneous injection or by catheter (see claims 25-26). Those of ordinary skill would have expected similar therapeutic results from the instantly claimed particle composition given the claims of US'265. There are no unusual and/or unexpected results, which would rebut prima facie obviousness. The instant claims would have been obvious given the claims of US'276.

This is a provisional obviousness-type double patenting rejection.

2. Claims 1, 3-15, 17-27, 29-33, and 35-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 11, 12, 22-45, and 48-51 of copending Application No. **10/637,130**. Although the conflicting claims are

not identical, they are not patentably distinct from each other because '276 was explained hereinabove while '130 recites a polymeric particle comprising a polyvinyl alcohol and having a diameter of about 500 microns or less, wherein the particle has a first density of pores in an interior region and a second density of pores at a surface region, the first density being different from the second density, and wherein the particle has a first average pore size in the interior region and a second average pore size at the surface region, the first average pore size being greater than the second average pore size. Accordingly, though '130 does not recite loading the particle with a therapeutic, '276 claims are within the scope of '130 and it is within the skill of an ordinary artisan to load the particles with a therapeutic agent comprising radioactive material.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Because of the large number of applications that Examiner reviewed and found to be overlapping in scope with the instant application as explained hereinabove, the Examiner cited the serial numbers of the applications that may overlap with the scope of claim 1 of the instant application, however, Applicant can argue the rejection when applicable.

3. Claims 1, 3-15, 17-27, 29-33, and 35-37 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Applications No. 10/215594, 10/232265, 10231664, 10651475, 10/858253 10/928452, 11/555413. Although the conflicting claims are not identical, they are not patentably distinct from each other because these applications are overlapping with the scope of polyvinyl particles that has two regions with two different densities of pores.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

3. Applicant's arguments filed 10/30/07 have been fully considered but they are not persuasive. **Applicant argues that:**

- One skilled in the art would understand that, Smith's process does not involve forming a cross-linked polymer matrix.

To respond: Smith teaches that the polymer is selected from polycarbonates, polyamides, polyurethanes acrylic resins, polystyrene, polyolefin's, cellulose acetate and other cellulosic esters, ethylenevinyl alcohols (note that ethyleneviny alcohol particles are used as equivalents to polyvinyl alcohol particles), and derivatives and copolymers of the above. Accordingly, a person of ordinary skill in the art would have finite number of derivatives to try and find the right derivative of the polymers. In addition. Gray teaches that in a preferred embodiment the polymeric matrix is partially cross linked (page 6, lines 8+).

- The solvent in Smith must be very carefully followed in order to obtain his particles.

would not have been obvious to one of ordinary skill in the art to try to modify Smith's process to try to obtain the particles covered by the pending claims, and, even if such a person had tried to do so, the evidence of record (i.e., Smith's own disclosure) indicates that failure would have been the result.

To respond: Applicant alleges that if a person of ordinary skill in the art try to modify Smith, Smith's own disclosure indicates that failure would have been the result, however, Applicant did not refer the Office to the citation of this specific disclosure. It is nowhere in Smith that the disclosure cannot be modified. Further, following the solvents and the rules of using the solvents as disclosed in Smith is a usual chemical instruction that have never stopped people having skill in the art from modifying different disclosures.

- Nowhere does Gray teach how to make his ion exchanges resin particles. Nor do Gray's particles have a first region including pores having a first predominant pore size and a second region surrounding the first region and including pores having a second predominant pore size, where the first predominant pore size is larger than the second predominant pore size.

To respond: even if Gray does not teach how to make his ion exchange resin particles; however, instant claims, although reciting a method of making composition ... (claim 27), it does not recite one step. Gray is relied upon for teaching particulate material having a diameter in the range of from 5 to 200 microns (page 6) comprising a polymeric matrix and stably incorporated radionuclide, such as radioactive yttrium (page 1), processes wherein radioisotope molecule is enclosed into the polymer bead (example 1).

- One skilled in the art would not have wanted to combine Smith's process with Gray's process to somehow obtain the particles covered by the pending claims.

To respond: It would have been obvious to one of ordinary skill in the art to comprise a radionuclide such as yttrium to the anisotropic structure of Smith because Smith teaches that asymmetric microporous beads are provided that can be prepared prior to loading them with active ingredient, that can contain up to 90% active ingredient, that are exceptionally durable, and that can release essentially all of the active ingredient at a constant rate over long periods of time (col. 2, lines 18+).

- Kaminski does not disclose or render obvious particles that include a cross-linked polymer matrix, where the particles also include a first region including pores having a first predominant pore size and a second region surrounding the first region and including pores having a second predominant pore size, and the first predominant pore size is larger than the second predominant pore size.

To respond: Applicant alleges that Kaminski does not render the instant claims obvious but does not demonstrate why. Kaminski et al. was relied upon because it teaches a radioactively labeled monoclonal antibody or radioactively labeled monoclonal antibody fragment wherein said antibody or said antibody fragment binds to CD20 antigen present on the surface of cells (claim 1).

- Ajay does not cure the deficiencies of Smith and/or Gray. None of Smith, Gray, or Ajay, discloses or renders obvious the particles covered by claims 11-12, and there is no suggestion to combine these references to provide the particles covered by these claims.

To respond: Ajay was relied upon for teaching the evaluation of the efficacy of preoperative meningioma devascularization with small polyvinyl alcohol (PVA) particles. The PVA particles are 150- 300 microns. It would have been obvious to one of ordinary skill in the art to use Polyvinyl particles as a carrier for a radioisotope which may be attached to an antibody and use it for other types of cancers like gastrointestinal, lung, thyroid, or breast cancers and apply it to the anisotropic pore structure of Smith. The motivation would be the disclosed results of Ajay, which demonstrates that, the angiography after embolization using polyvinyl alcohol demonstrated the total elimination of tumor blush in all patients.

- Atcher does not cure the deficiencies of Smith and/or Gray. None of Smith, Gray, or Atcher, discloses or renders obvious the particles covered by claims 13-14 and 32, and there is no suggestion to combine these references to provide the particles covered by these claims.

To respond: Atcher was relied upon to obviate a labeled colloid which is useful in cancer therapy and for the treatment of inflamed joints. A colloid is defined as a system in which finely divided particles, which are approximately 10 to 10,000 angstroms in size, are dispersed within a continuous medium in a manner that prevents them from being filtered easily or settled rapidly. Since Atcher describes a colloid, which is according to, the definition made of particles.

It is understood that the radioisotope is attached to the outer surface of the particles (abstract).Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to develop a particle made of a polymer in an anisotropic pore structure like Smith's and attach the radionuclide because Atcher discloses that the surface attached radionuclides can be used in cancer therapy. The artisan would have a good expectation of success of preparing a particle wherein a radionuclide is laid on the surface of the particle.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618